Primordial germ cells and gastrointestinal stromal tumors respond distinctly to a cKit overactivating allele.

Journal: Hum Mol Genet

Publication Year: 2013

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PubMed link: 23077213

Funding Grants: SFSU Bridges to Stem Cell Research

Public Summary:
KitL, via its receptor cKit, supports primordial germ cell (PGC) growth, survival, migration and reprogramming to pluripotent embryonic germ cells (EGCs). However, the signaling downstream of KitL and its regulation in PGCs remain unclear. A constitutively activating mutation, cKit(V558Δ), causes gain-of-function phenotypes in mast cells and intestines, and gastrointestinal stromal tumors (GISTs) when heterozygous. Unexpectedly, we find that PGC growth is not significantly affected in cKit(V558Δ) heterozygotes, whereas in homozygotes, increased apoptosis and inefficient migration lead to the depletion of PGCs. Through genetic studies, we reveal that this oncogenic cKit allele exhibits loss-of-function behavior in PGCs distinct from that in GIST development. Examination of downstream signaling in GISTs from cKit(V558Δ/+) mice confirmed hyperphosphorylation of AKT and ERK, but both remain unperturbed in cKit(V558Δ/+) PGCs and EGCs. In contrast, we find reduced activation of ERK1/2 and JNK1 in cKit(V558Δ) homozygous PGCs and EGCs. Inhibiting JNK, though not ERK1/2, increased apoptosis of wild-type PGCs, but did not further affect the already elevated apoptosis of cKit(V558Δ)(/V558Δ) PGCs. These results demonstrate a cell-context-dependent response to the cKit(V558Δ) mutation. We propose that AKT overload protection and JNK-mediated survival comprise PGC-specific mechanisms for regulating cKit signaling.

Scientific Abstract:
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